

Crystal structure of human cytosolic phospholipase A₂ reveals a novel topology and catalytic mechanism

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Cytosolic phospholipase A₂ initiates the biosynthesis of prostaglandins, leukotrienes, and platelet-activating factor (PAF), mediators of the pathophysiology of asthma and arthritis. Here we report the x-ray crystal structure of human cPLA₂ at 2.5 Å solved using multiwavelength anomalous dispersion (MAD) phasing. cPLA₂ consists of an N-terminal calcium-dependent lipid binding/C2 domain and a catalytic unit whose topology is distinct from that of other lipases. An unusual Ser-Asp dyad located in a deep cleft at the center of a predominantly hydrophobic funnel selectively cleaves arachidonyl phospholipids. The structure reveals a flexible lid which must move to allow substrate access to the active site, thus explaining the interfacial activation of this important lipase.

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